REMARKS

Status of the Claims

Claims 13-17 are new. Support for the new claims can be found throughout the present specification and claims as originally filed, e.g., page 3, lines 2-24. No new matter has been added.

Now pending are claims 1, 4, 5, 7-10 and 13-17.

Rejections under 35 U.S.C. §103(a)

In the Office Action, claims 1, 5, 7, and 10 stand rejected as unpatentable over Patel et al. (U.S. Patent No. 5,340,572). This rejection is traversed.

According to the Office Action, Patel "[teaches] a topical gel composition containing medicaments . . . . Diclofenac is disclosed . . . . Ammonium chloride at 0.01 – 5% is specified . . . Sustained efficacy is disclosed." Office Action at page 2. The Office Action concludes, "It would have been obvious . . . to make a composition comprising a gel including diclofenac and ammonium chloride to achieve the beneficial effect of sustained efficacy in view of Patel et al." Applicants respectfully disagree.

As an initial matter, it must be pointed out that Patel is directed to ophthalmic formulations, not to percutaneously absorbable preparations as in the present claims.

In addition, although Patel mentions in passing the use of "diclofenac," Applicants respectfully contend that Patel does not disclose the use of sodium diclofenac as recited in the present claims. It will be appreciated that diclofenac and sodium diclofenac are different and may have different properties; for example, the absorbability of the two materials in a percutaneously absorbable preparation is not the same. Although the Office Action states that "sodium diclofenac is the diclofenac of commerce" (Office Action at page 2), the Office Action provides no evidence for this statement and does

not suggest that Patel discloses sodium diclofenac (as opposed to other salt forms or the free acid of diclofenac).

Furthermore, while the Office Action refers to Patel at column 8, lines 19-38 as disclosing the use of "[a]mmonium chloride at 0.01-5%," Applicants point out that the cited portion of Patel does not disclose the use of ammonium chloride as cited by the Examiner. The only mention of ammonium chloride in Patel is in a listing of buffers at column 8, lines 14-15 (where no amounts are provided). In fact, Patel, at column 8, lines 30-39, provides that:

> Equivalent amounts of one or more salts made up of cations such as potassium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfite and the like, e.g., potassium chloride, sodium thiosulfate, sodium metabiosulfite, sodium bisulfite, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the above-stated ranges.

Applicants submit that this generalized recitation of cations and anions, and certain specific salts other than ammonium chloride, does not constitute a disclosure of ammonium chloride. The list of possible cations and anions in the above-quoted passage is large (i.e., at least potassium, ammonium, and sodium as cations, and at least 10 recited anions). This general disclosure, with a large number of possible combinations and no specific disclosure of ammonium chloride, does not (contrary to the Office Action at pages 2-3) teach or suggest the specific salt, ammonium chloride, especially in view of the statement in Patel that "sodium chloride is preferred" (Col. 8, line 24). Further, although the Office Action states that Patel teaches "the molar range of . . . ammonium chloride is 0.002 – 0.3 moles /per liter," no amount of ammonium chloride is specifically stated.

The salts disclosed at the cited portion of Patel are used to provide a desired osmolality of the ophthalmic formulation. Applicants contend that such a disclosure is not relevant to the absorbability of sodium diclofenac, and is not relevant to the patentability of the present claims. Although the Office Action states that "[a]n optimum suitable range is obtained by routine experimentation," Office Action at page 2, one of ordinary skill in the art would not have been motivated by Patel to prepare a preparation according to the present claims. Indeed, one of ordinary skill in the art would not be motivated to select the specific combination of sodium diclofenac and ammonium chloride, in the recited amounts, as required by the pending claims.

Still further, although the Office Action stated that it would have been obvious to make a composition comprising a gel including diclofenac and ammonium chloride to sustained efficacy in view of Patel et al., the composition of Patel provides sustained efficacy by remaining in gel form in the eye for an extended period. Applicants contend that it is unlikely that ammonium chloride would be used in a sustained-release ophthalmic formulation due to the irritant properties of ammonium chloride.

The Office Action states that "applicants argue intended use." This is incorrect. Applicants simply contend that the Patel reference is not relevant to the claimed invention, and that one of ordinary skill in the art would not have been motivated to modify the Patel reference as suggested by the Office Action. Applicants contend that the Office Action has not established a *prima facie* case of obviousness in view of the Patel reference.

Moreover, Applicants submit that any *prima facie* case of obviousness is rebutted by evidence of the unexpected properties of the claimed percutaneous preparations. As seen from the Examples provided in the specification, preparations including ammonium chloride in addition to sodium diclofenac have enhanced skin permeability compared to preparations having no ammonium chloride. See, e.g., Example 4 (about 7-fold increase in skin permeability rate with ammonium chloride compared to Comparative

Example 4 without ammonium chloride) and Example 19 (about 4.8-fold increase in skin permeability rate with ammonium chloride compared to Comparative Example 19 without ammonium chloride). Applicants submit that such unexpectedly superior properties are not and cannot be obvious, and that the presently-claimed preparations (and the methods of new claims 13-17) are not clearly not obvious in view of the cited reference.

For at least the foregoing reasons, Applicants contend that the pending claims are not rendered unpatentable by Patel et al.

In the Office Action, claims 1, 4, 5, and 7-10 stand rejected as unpatentable over Ledger et al. (U.S. Patent No. 5,120,545) in view of Inagi. This rejection is traversed.

According to the Office Action, Ledger "[teaches] a matrix for transdermal administration of a drug . . . Ammonium chloride is specified . . . Analgesic agents including ketoprofen are disclosed." Office Action at page 3. The Office Action concludes, "It would have been obvious . . . to make a matrix comprising an analgesic such as ibuprofen and ammonium chloride to achieve the beneficial effect of reducing sensitization." The Office Action further states that

> it would have been further obvious to use diclofenac as the analgesic and acrylic as an adhesive in the composition of Ledger et al. in view of the fact that the former is known in the art as equivalent to ibuprofen and the latter is known in the art as an adhesive in view of Inagi et al.
>
> Office Action at page 3. Applicants do not agree.

As previously noted, Ledger does not disclose ibuprofen or diclofenac, although ketoprofen is mentioned. Ledger mentions ammonium chloride as a weak base to raise the pH within lysosomes, as an antigen processing-inhibiting agent. Applicants submit that this is not relevant to the presently-claimed percutaneously absorbable

preparations. The disclosure of Ledger cannot render obvious the presently-claimed percutaneously absorbable preparation.

Although the Office Action states that Inagi teaches "the equivalence of ketoprofen to diclofenac as an analgesic" (Office Action at page 3), neither Inagi nor Ledger teaches that diclofenac is a "sensitizing drug" as that term is used in Ledger, i.e., a drug that "tends to cause contact sensitivity or contact allergy to a human as a result of antigenic sensitization following transdermal application of the compound to the skin or mucosa". Even if Inagi teaches "the equivalence of ketoprofen to diclofenac as an analgesic" as stated in the Office Action (which Applicants do not concede, as Inagi merely lists a number of agents), there would be no motivation to modify the teachings of Ledger as suggested by the Office Action, because there is no teaching or suggestion that is a "sensitizing drug" as that term is used in Ledger.

Furthermore, Inagi is directed to hydrophilic adhesive base materials having excellent mechanical strength and adhesion to skin. There would be no motivation to combine the teachings of Ledger (even if the teachings as were as described by the Examiner) with the teachings of Inagi to arrive at the presently-claimed percutaneously absorbable preparations. Ledger and Inagi are directed to different objectives, and there would simply be no reason to combine the references as suggested in the Office Action. Moreover, Applicants submit that there would be no reasonable expectation of success in making such a combination to arrive at the presently-claimed percutaneously absorbable preparations.

Still further, as discussed above, Applicants submit that any *prima facie* case of obviousness is rebutted by evidence of the unexpected properties of the claimed percutaneous preparations. As discussed above, preparations including ammonium chloride in addition to sodium diclofenac have enhanced skin permeability compared to preparations having no ammonium chloride. Applicants submit that such unexpectedly superior properties are not and cannot be obvious, and that the presently-claimed

preparations (and the methods of new claims 13-17) are not clearly not obvious in view of the cited references.

For at least the foregoing reasons, Applicants contend that the pending claims are not rendered unpatentable by Ledger or Inagi, alone or in combination.

Reconsideration and withdrawal of the rejections is proper and such action is requested.

New claims

New claims 13-17 are directed to methods for improving the percutaneous absorbability of sodium diclofenac, by providing ammonium chloride in the preparation at a range of from 0.5 to 10 fold mole/mole based on the sodium diclofenac.

As discussed above, none of the references cited in the Office Action renders obvious claims to preparations, or methods of making preparations, having improved percutaneous absorbability of sodium diclofenac. Therefore, for at least the reasons discussed above, none of the references, alone or in combination, render obvious the new claims.

Conclusion

For at least the foregoing reasons, Applicants request reconsideration of the application. Early and favorable action is requested.

Applicants request any extension of time necessary for consideration of this response. If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**, under Reference No. 56769 (71526), Customer No. 21874.

Respectfully submitted,

Date: April 28, 2008

/Mark D. Russett/

Mark D. Russett, Reg. No. 41,281
EDWARDS ANGELL PALMER & DODGE LLP
P. O. Box 55874
Boston, MA 02205
Tel: (617) 239-0100
Fax: (617) 439-4170